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Hepatic Failure: An Evidence-Based Approach In The Emergency Department

On a typical swing shift, your ED is full of patients with a chief complaint listed as "abdominal pain." You go in to see one such patient, a 40-year-old male, after his nurse tells you he "does not look very good." He states that he has had gradually worsening abdominal pain for over a week, and that today he felt so fatigued he was unable to go to work. Before this, he was otherwise healthy, and no one around him has been sick. On further history, he reveals that 6 weeks ago he was started on isoniazid for a positive PPD (tuberculosis) test in the absence of active chest disease. Other than mild tachycardia (to 112 beats per minute), his vital signs are normal. Physical examination reveals that his sclerae are yellow and detects marked tenderness of the right upper quadrant with mild hepatomegaly. His wife tells you she is concerned because he seems confused.

You are interrupted by a call to the resuscitation bay to evaluate a patient whose blood pressure is 78/37 mm Hg. You recognize him because of his frequent visits to the ED for tense ascites requiring large-volume paracenteses. EMS reports that twice during transit he vomited dark-red blood. He is pale and diaphoretic. This patient is obviously critically ill, and it is clear your next steps will determine his outcome.

Hepatic failure presents with a variety of acute manifestations, most of which will be seen at some point during the ED clinician's career. At the most critical end of the spectrum is the syndrome of acute liver failure (ALF), in which hepatic function is suddenly lost in a person with no previous liver dysfunction. Cur-

April 2010
Volume 12, Number 4

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CME Objectives

Upon completion of this article, you should be able to:

1. Recognize and diagnose acute liver failure (ALF).
2. Describe the underlying etiologies of ALF.
3. Explain the ED approach to complications of chronic liver failure (CLF).
4. Discuss the overall care and disposition of critically ill patients with liver failure.

Date of original release: April 1, 2010
Date of most recent review: December 1, 2009
Termination date: April 1, 2013
Medium: Print and Online
Method of participation: Print or online answer form and evaluation
Prior to beginning this activity, see "Physician CME Information" on the back page.

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Accreditation: EB Medicine is accredited by the ACCME to provide continuing medical education for physicians. **Faculty Disclosure:** Dr. Bailey, Dr. Hern, Dr. Ortega, Dr. Sacchetti, Dr. Strayer, and their related parties report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation. **Commercial Support:** This issue of *Emergency Medicine Practice* did not receive any commercial support.

rently, the most widely accepted definition of ALF is the presence of both coagulopathy (international normalized ratio [INR] > 1.5) and altered mental status consistent with hepatic encephalopathy of less than 26 weeks' duration (a change from the previously defined timeline of 8 weeks).[1,2] This disorder is rare, with an annual incidence in the US of 2300 to 2800 cases, and results in 0.1% of all deaths and 6% of all liver-related deaths in the US.[3,4] However, this condition can deteriorate rapidly and is associated with high morbidity and mortality. Precipitating etiologies must be quickly identified and disease-specific interventions implemented in order to prevent further decompensation or death. Early transfer to a tertiary care facility with transplant capability may also be necessary.

More common than ALF is chronic liver failure (CLF) with cirrhosis, the 12th leading cause of death in the US.[5] While primarily a disorder of long-term outpatient management, acute decompensation of CLF may bring the patient to the ED because of variceal hemorrhage, symptomatic ascites, spontaneous bacterial peritonitis, hepatorenal or hepatopulmonary syndrome, and hepatic encephalopathy. The ED clinician must confront these manifestations and guide management within the broader context of the patient's chronic care.

This issue of *Emergency Medicine Practice* focuses on the management of ALF and the acutely symptomatic cirrhotic patient.

Critical Appraisal Of The Literature

A literature search was performed using the following databases: Ovid MEDLINE® (www.ovid.com) and PubMed (www.pubmed.gov) the Cochrane Database of Systematic Reviews, the National Guideline Clearinghouse, the Agency for Health Care Research and Quality Clinical Guidelines and Evidence Reports, and EBM Online/Evidence-Based Medicine. Searches were limited to the English language and to studies involving adult human subjects. In addition, we examined selected studies drawn from the bibliographies found in the literature. The search yielded many review articles and descriptive studies but few randomized, controlled trials regarding acute hepatic failure. For this reason, the American Association for the Study of Liver Diseases (AASLD), which publishes practice guidelines for many specific hepatologic disorders, presented its recommendations for ALF in the form of a position paper expressly stating that the available data are not sufficient to support a formal practice guideline.[6] Significantly more data are available regarding the complications of chronic cirrhosis. Some nationally published guidelines regarding acute hepatic injury are available. **Table 1** lists selected guidelines for hepatic injury relevant to the ED setting.

Table 1. Relevant Practice Guidelines For ED Management Of Hepatic Injury

Organization	Topic	Type	Recommendations
American Association for the Study of Liver Diseases (AASLD)[7]	Ascites due to cirrhosis	Evidence-based	• Abdominal paracentesis should be performed for patients with clinically apparent ascites of new onset • Prophylactic use of FFP or platelets before paracentesis is not recommended • Initial lab investigation of ascitic fluid should include a CBC with differential, total protein, and serum-ascites albumin gradient • If infection is suspected, ascitic fluid should be cultured
AASLD and the American College of Gastroenterology (joint)[8]	Hemorrhage from esophageal varices in cirrhosis	Evidence-based	• Short-term antibiotic prophylaxis should be prescribed in any patient with cirrhosis and GI hemorrhage (**See Table 10, page 12 for regimens**) • Pharmacologic therapy should be initiated as soon as variceal hemorrhage is suspected (**See Table 11, page 16 for regimens**) • EGD should be performed within 12 hours to diagnose and treat variceal hemorrhage • TIPS is indicated in patients in whom variceal hemorrhage cannot be controlled or in cases of rebleeding despite therapy • Balloon tamponade is indicated as a temporizing measure (within 24 hours) in patients with uncontrollable hemorrhage for whom more definitive therapy is planned
AASLD and the American College of Gastroenterology (joint)[8]	Hemorrhage from gastric varices in cirrhosis	Evidence-based	• Endoscopic variceal obturation with tissue adhesive is preferred for gastric fundal variceal bleeding; if unavailable, ligation can be performed • TIPS is an alternative for patients with uncontrolled fundal variceal bleeding or recurrent bleeding

Abbreviations: EGD, esophagogastroduodenoscopy; FFP, fresh frozen plasma; TIPS, transjugular intrahepatic portosystemic shunt.

Etiology And Pathophysiology

Acute Liver Failure

ALF is characterized by severe dysfunction of damaged hepatocytes, which renders these cells less capable of carrying out their synthetic and degradative roles. These effects are manifest as coagulopathy and hypoalbuminemia, as well as the accumulation of harmful metabolites.

The disparate causes of ALF have crucial implications for prognosis as well as intervention. In recent decades, acetaminophen toxicity and idiosyncratic drug reactions have replaced viral hepatitis as the most common causes of ALF in the US.[9] When viral hepatitis is responsible, the overwhelming culprits are the hepatitis A and B viruses; hepatitis D rarely causes ALF in patients infected with hepatitis B, and hepatitis E is more likely in developing countries and among pregnant women. Hepatitis C rarely, if ever, causes ALF; although it was not identified in a prospective study of viral hepatitis–related ALF in the US,[10] it has been implicated in a small series of studies from Asian countries.[11,12] Other causes of ALF include inborn errors of metabolism, ischemic insult, Wilson disease,[13] malignancy,[14] other viruses (herpes simplex, Epstein-Barr, paramyxovirus), nonpharmacologic toxins such as *Amanita* (mushroom) poisoning[15]; rarely, acute fatty liver of pregnancy,[16] Budd-Chiari syndrome,[17] connective tissue disorders,[18] and autoimmune hepatitis are responsible for ALF.[19] Finally, there have been case reports of ALF occurring secondary to cardiac trauma and seizures.[20,21] In approximately 15% of adult cases, no cause is ever found. **Figure 1** shows the most common causes of ALF based on a study of 1147 adults by the US ALF Study Group from 1998 to 2007.[13]

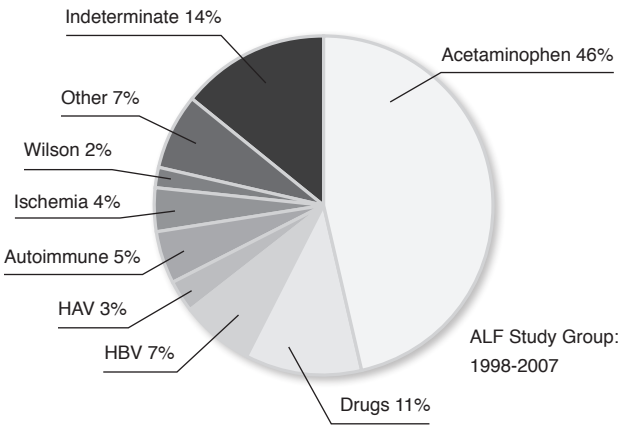
The pathophysiology of ALF clearly varies with the cause; however, in drug-induced hepatic injury, the pathophysiology has significant implications for management. Drugs can harm the liver in either a dose-related or a nondose-related (idiosyncratic) fashion, the latter being characterized by latency in effect and rarity of occurrence. Idiosyncratic drug reactions typically occur within 6 months after treatment has begun and rarely occur beyond a year of continuous use.

The prototypical dose-related hepatotoxin is acetaminophen (also known as paracetamol, APAP). When taken in amounts that overwhelm the safe metabolic pathways of glucuronidation and sulfation, acetaminophen is metabolized to the toxic compound N-acetyl-p-benzoquinone-imine (NAPQI) via the cytochrome P-450 system. Drugs and other toxins can also induce hepatic enzymes, leading to secondary hepatotoxicity from other substances. The interaction between ethanol and acetaminophen is the prototypical example of this. Acute ingestion of ethanol with acetaminophen can protect against its toxicity, since ethanol competes for the enzymatic activity of cytochrome P-450 (CYP2E1 isoenzyme), making this pathway less available for the metabolism of acetaminophen. However, ethanol also induces CYP2E1 activity and prevents the degradation of this isoform, thus increasing its availability to metabolize acetaminophen once ethanol is no longer present. The chronic use of ethanol predisposes to acetaminophen toxicity, a fact that has implications for the safety of acetaminophen in alcohol abusers. In a case series of patients who developed hepatic injury from acetaminophen taken for therapeutic relief rather than intentional ingestion, 64% were considered alcoholic. The majority of acetaminophen doses in this group were considered "nontoxic" for the average adult.[22]

Idiosyncratic reactions to drugs can harm the liver through a variety of mechanisms, including their covalent binding to intracellular proteins, provocation of an autoimmune response, damage to mitochondria, activation of apoptosis, and general circulatory collapse.[23] Based on the general mechanism, the pattern of injury with particular drugs may be predominantly hepatocellular, cholestatic, or mixed, which will alter the pattern of abnormality seen on laboratory testing.[24] **See Table 2, page 4** for a list of examples of hepatotoxic compounds.

Over-the-counter herbal supplements have also been associated with hepatotoxicity.[25] ALF from drug-related hepatotoxicity is associated with decreased survival without transplantation, so early recognition is critical.

Figure 1. Etiology Of ALF In Adults



Chronic Liver Failure

The unifying pathophysiology underlying most complications of chronic liver disease is cirrhosis, the development of fibrous tissue and regenerative nodules in place of normally functioning hepatic

tissue. Venous flow into the liver decreases as a consequence of this architectural change, leading to elevated portal pressures. Portal hypertension then leads to splenomegaly, which causes anemia and thrombocytopenia via increased sequestration and destruction of red blood cells and platelets.

Ascites

Elevated hydrostatic pressure within the portal vasculature causes ascites via the extravasation of extracellular fluid from the portal system into the peritoneal space down a pressure gradient. Hypoalbuminemia from decreased hepatic synthetic capacity lowers the oncotic pressure in the vasculature, worsening fluid egress. Accumulated peritoneal fluid can in turn exert pressure on intra-abdominal organs such as the kidney, decreasing the glomerular filtration rate, which further lowers the excretion of sodium and water via activation of the renin-angiotensin-aldosterone feedback loop and anti-diuretic hormone, which in turn leads to exacerbation of ascites via fluid overload. The resulting intraperitoneal fluid causes uncomfortable abdominal distension.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) occurs when acute renal failure develops in the setting of liver failure in a patient with otherwise normal kidneys. Although this syndrome is more common in patients with advanced cirrhosis, it can also occur in acute hepatic failure. It is caused by extreme renal artery vasoconstriction in the setting of splanchnic vasodilatation, a low effective plasma volume, and insufficient cardiac output. The following criteria developed by the International Ascites Club[26,27] define hepatorenal syndrome:

1. Cirrhosis with ascites
2. Creatinine > 1.5 mg/dL (133 µmol/L)
3. No improvement of serum creatinine within 2 days of diuretic withdrawal and volume expansion with albumin (recommended dose 1 g/kg (max 100 g/day)
4. Absence of shock
5. No current or recent treatment with nephrotoxins
6. Absence of parenchymal kidney disease (proteinuria > 500 mg/day, microhematuria, abnormality on renal ultrasonography)

These criteria have been updated to include the new recommendation to use albumin instead of saline for volume expansion and to broaden the criteria to include acutely infected patients without evidence of shock.

Type I hepatorenal syndrome is defined as the rapid loss of renal function over less than 2 weeks (doubling of initial creatinine to Cr > 2.5 mg/dL), whereas type II does not involve such a sudden change. Type I is often provoked by an acute insult such as spontaneous bacterial peritonitis (SBP) and is associated with an extremely high mortality, with 1 series reporting a median survival of 3.3 months.[28]

Hepatopulmonary Syndrome

Tense ascites can extravasate across the diaphragm to cause pleural effusions that subsequently compress the lungs, causing dyspnea and hypoxia. However, true hepatopulmonary syndrome is a disorder of pulmonary vascular dilatation (precapillary and capillary) and shunting thought to be secondary to vasoactive factors such as nitric oxide.[29] This dilatation causes severe arterial hypoxemia through

Table 2. Drugs And Toxins That Can Damage The Liver

Acarbose	MDMA
Acetaminophen	Methimazole
Acetylsalicylic acid	Methotrexate
Allopurinol	Methyldopa
Amanita phalloides and related mushrooms	Minocycline
Amiodarone	Mirtazapine
Amitriptyline	Nefazodone
Amoxicillin—clavulanic acid	Nicotinic acid
Antiretroviral agents	Nitrofurantoin
Arsenic	NSAIDs
Azathioprine	Omeprazole
Baclofen	Paroxetine
Buproprion	Pennyroyal oil
Captopril	Phenobarbital
Carbamazepine	Phenol
Carbon tetrachloride, other chlorinated hydrocarbons	Phenothiazines
Chlorpromazine	Phenytoin
Clindamycin	Phosphorus
Clopidogrel	PCBs
Cocaine	Propylthiouracil
Copper	Pyrazinamide
Cyclosporine	Pyrrolizidine alkaloids
Diclofenac	Quinidine
Diltiazem	Rifampin
Disulfiram	Risperidone
Enalapril	Sertraline
Estrogen	Statins
Erythromycin	Sulfa derivatives
Fluoxetine	Tamoxifen
Gyromitra mushrooms	Terbinafine
Halothane	Tetracycline
Irbesartan	Thallium
Iron	Trazodone
Isoniazid	Tricyclic antidepressants
Ketoconazole	Troglitazone
Lisinopril	Valproic acid
Losartan	Venlafaxine
	Verapamil
	Vitamin A

Abbreviations: MDMA, 3,4-methylenedioxy-methamphetamine; NSAID, Nonsteroidal anti-inflammatory agents; PCBs, polychlorinated biphenyls.

a combination of ventilation-perfusion mismatch, shunting, and impaired diffusion. Diagnostic criteria therefore include the triad of chronic liver disease, arterial deoxygenation, and intrapulmonary vasodilatation, with severity of this syndrome graded according to the alveolar-arterial oxygen gradient or partial pressure of oxygen. Although there is no strict correlation between the degree of liver disease and the presence of this syndrome, it is associated with significantly increased mortality for each stage of liver disease. Overall, it carries a grave prognosis, with a median survival as low as 11 months in 1 cohort,[30] and an overall 5-year survival rate of 23% without transplantation.[31] For these reasons, the AASLD recommends expedited referral and evaluation for transplantation for patients with hepatopulmonary syndrome[32] Orthotopic liver transplantation is the only successful treatment available.

Variceal Hemorrhage

Elevated portal pressures also lead to the development of portosystemic collaterals such as varices, which are dilated vessels within the esophagus, stomach, and colon. The most common cause of death associated with cirrhosis is rupture of gastroesophageal varices and ensuing hemorrhage. The risk of rupture is proportional to variceal wall tension, which is most directly related to the size of the varix.

Hepatic Encephalopathy

Hepatic encephalopathy occurs with both acute and chronic liver failure but is more common and rapidly progressive in ALF. It results from hepatocellular damage, which prevents the liver from metabolizing waste products in the blood, including nitrogenous compounds such as ammonia. Although the exact pathophysiology is unknown, it is postulated that these compounds may be structurally similar to neurotransmitters, causing dysfunctional neural transmission with associated altered mental status and motor abnormalities such as asterixis, the repetitive clonic flexion of the wrist when maintained in hyperextension. **Table 3** shows the grades of hepatic encephalopathy.

Table 3. Grades Of Hepatic Encephalopathy

I	Changes in behavior with minimal change in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

Adapted by the American Association for the Study of Liver Diseases from criteria of Conn et al.[33]

Cerebral edema with elevated intracranial pressure is associated with hepatic encephalopathy (with increasing frequency at higher grades) and is a common cause of death.[34] Some evidence suggests that ammonia levels do not correlate with degree of hepatic encephalopathy in general,[35] although cerebral edema has been induced by ammonia infusion in a rat model,[36] and in 1 human study ammonia levels greater than 200 µg/dL were associated with cerebral herniation.[37]

Differential Diagnosis

The differential diagnosis for ALF should include other potential causes of altered mental status as well as other etiologies of abdominal pain, jaundice, or a clinically evident bleeding diathesis. (**See Table 4.**) The morbidity of altered mental status varies depending on the cause; some otherwise benign etiologies, such as alcohol intoxication, can be life-threatening when encountered in the extreme (eg, combined alcohol and benzodiazepine ingestion with depressed respiratory drive). In patients with acute upper gastrointestinal bleeding, alternative diagnoses must be considered if there is no known history of cirrhosis. (**See Table 5.**) The ED clinician must rapidly consider life-threatening causes of such presentations while simultaneously initiating stabilizing measures.

Table 4. Differential Diagnosis For Patients With Altered Mental Status

- Hypoglycemia
- Hypoxia (pulmonary embolism, acute coronary syndromes, pneumonia)
- Intracerebral hemorrhage, spontaneous or traumatic
- Meningitis/encephalitis
- Cerebrovascular accident
- Intracranial mass
- Severe intoxication (opiates, barbiturates, alcohol)
- Myxedema coma
- Wernicke encephalopathy
- Sepsis
- Seizure, postictal state
- Chronic dementia
- Uremia
- Hyponatremia or hypernatremia

Table 5. Differential Diagnosis For Patients With Gastrointestinal Bleeding

- Ulcer disease
- Gastritis
- Mallory-Weiss tear
- Boerhaave syndrome
- Aortoenteric fistula

Prehospital Care

For most patients with hepatic failure, prehospital care requirements are minimal. For the patient with upper gastrointestinal (GI) bleeding, prehospital care goals include the establishment of large-bore intravenous (IV) access, careful monitoring of the airway in the event of further emesis, and contact with base control if vital signs are unstable so that arrangements with the blood bank can be made in advance of the patient's arrival. Universal precautions should be strictly observed in every case, but the likelihood of viral hepatitis in patients with liver failure further emphasizes the importance of personal protective equipment.

ED Evaluation

Triage And Initial Stabilization

Depending on the presenting complaint, patients with liver failure may be clinically stable but can deteriorate quickly. When appraising vital signs, the ED clinician should pay close attention to the patient's medication regimen, since many patients with cirrhosis will be taking nonselective beta-blockers that may blunt the normal tachycardic response to bleeding. Patients with a decreased level of consciousness should be evaluated for intubation. Large-bore IV access should be established if it is not already in place, with preference given to peripheral access both to allow rapid resuscitation and to avoid the morbidity associated with central access in patients with potential coagulopathy. If necessary, central access should be established at compressible sites under ultrasound guidance if acuity permits. Patients who report bloody or dark-colored emesis, melena, hematochezia, or altered mental status should be triaged to high-visibility beds with cardiac monitoring capability. Almost all complaints related to liver failure — abdominal pain, nausea or vomiting, bleeding, distention, shortness of breath, altered mental status, jaundice — require laboratory evaluation, so these patients are not candidates for provider-in-triage or other fast-track disposition.

History

Because acute and chronic liver failure differ significantly in etiologies, complications, and morbidity rates, the approach to the patient suspected of having hepatic failure must focus initially on determining the timing of symptom onset.

If the timing is consistent with ALF, questions should pertain to all the medications the patient is currently taking, including prescription drugs and over-the-counter medications. Particular attention should be paid to the ingestion of acetaminophen to establish quantity and timing, as well as herbal supplements, mushrooms, and plant or tea extracts, In addition, the ED clinician should elicit any history of alcohol and recreational drug use (especially if administered intravenously or by skin popping), recent travel, sexual exposures, needlestick exposures, blood transfusions, exposure to industrial compounds, recent anesthesia or illness that required hospitalization, and any family history of liver disease or autoimmune disease. Information from collateral sources such as family and caregivers should be sought regarding any subtle changes in the patient's mental status consistent with early-stage encephalopathy. A history of light-colored stools or dark urine can be clues to cholestasis in the absence of overt jaundice.

If the onset of symptoms is more consistent with CLF or a known diagnosis of cirrhosis, assessments should include the patient's current management regimen (medications and degree of compliance, endoscopic assessment showing the presence or absence of varices, frequency of follow-up visits), as well as the presence of anorexia and weight loss or pruritus (due to bilirubin deposition), and any history of paracentesis, previous SBP, or renal dysfunction. Further history will be directed at the chief complaint: a complaint of worsening ascites should prompt the ED clinician to ask questions about associated symptoms such as shortness of breath, decreased exercise tolerance, abdominal pain, and fever/chills, as well as potential causes of decompensation such as dietary indiscretion.

Physical Examination

Physical examination should begin with an assessment of the patient's vital signs, mental status, and perfusion. In the grossly obtunded patient, the ED clinician should look for signs of impending herniation due to cerebral edema, such as loss of pupillary reflexes or the presence of Cushing's reflex (hypertension with bradycardia and abnormal respirations). Patients with liver failure are susceptible both to intravascular depletion with peripheral vasoconstriction (bleeding, dehydration from vomiting) and to sepsis with distributive physiology and vasodilatation (SBP).

In the stable patient, consider testing for low-grade encephalopathy with the Quick Confusion Scale, a 6-item, 15-point instrument designed for the rapid assessment of mental status. This scale has been shown to correlate fairly well with results on the Mini-Mental State Examination (MMSE) but requires less time to administer.[38]

To test for asterixis, ask the patient to raise both arms and hyperextend the wrists. Jaundice may be subtle and is best detected by examining the sclerae and the mucosa under the tongue. In patients with acute hepatitis, the abdominal examination will often reveal tender hepatomegaly, whereas patients with cirrhosis may have splenomegaly but will

not have a palpable liver. Tense ascites is typically self-evident, but less overt ascites can be difficult to diagnose on physical examination alone, with a sensitivity between 50% and 90% reported in 1 study.[39] Because the population is increasingly overweight, it is becoming more difficult to detect ascites. Point-of-care abdominal ultrasound to detect free fluid can aid in the diagnosis of ascites. **Table 6** lists several other findings in CLF.

Diagnostic Studies

Laboratory Evaluation

Virtually all patients with complaints related to liver failure will require laboratory testing. The traditional "liver function tests" are really a combination of tests that reflect hepatocellular injury and cholestasis. The goal of basic testing is to establish the degree of hepatocyte injury and impairment of synthetic function. Other tests are directed toward determining the causal agent of the liver injury, predicting further clinical decline, and detecting infection. The **Clinical Pathway For Evaluation Of Patients With Suspected Acute Hepatic Injury** (**see Page 10**) presents recommended approaches to laboratory testing, and **Table 7** offers interpretations of abnormal results on liver chemistry studies.

Aminotransferases

Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) are intracellular enzymes found in hepatic and other cells and are released into the bloodstream when hepatocytes are damaged. ALT is more specific to the liver than is AST, although both are found in other cells (ALT in the kidney, AST in the heart, skeletal muscle, and kidney).[41] The degree and patterns of elevation of these enzymes have diagnostic utility for the timing of injury in the patient with undifferentiated liver failure. AST and ALT are rarely elevated to greater than 10 times normal outside the setting of acute liver injury. The values of 200 U/L for AST and 300 U/L for ALT have discriminant value for acute hepatic injury, with respective sensitivities of 91% and 96% and specificities of 95% and 94%.[40] However, peak aminotransferase levels do not correlate with prognosis.[42]

Aminotransferase levels and the AST:ALT ratio can also help determine the etiology of ALF. Levels of both AST and ALT may be markedly elevated in acute ischemic injury but improve quickly once the patient's circulatory status has been stabilized. AST may reach extremely high levels (up to 48,000 U/L) in acetaminophen overdose, with 90% of patients with acetaminophen toxicity having values greater than 3000, according to one study.[22] An AST level of 3000 was highly associated with acetaminophen injury but not with alcoholic or acute viral hepatitis, although descriptive statistics were not reported. In cases of toxic hepatic injury (including acetaminophen overdose), AST and ALT levels typically decline quickly, with AST declining more rapidly because of its shorter half-life (17 hours vs 47 hours for ALT).[40] In cases of ALF related to viral hepatitis, an AST:ALT ratio of 0.6 or less was associated with spontaneous survival, especially for hepatitis A patients, though the included numbers were small and the observation empirical. The authors posit that this ratio may reflect a higher ALT level representing more hepatic tissue at baseline with improved reserved capacity, but this observation remains to be explored.[10]

Alkaline Phosphatase

Alkaline phosphatase (AP) is found in hepatic bile canaliculi, where it functions in membrane transport.[43] The production and release of AP is stimulated by cholestasis, ie, the failure of bile to exit the

Table 6. Physical Findings In Liver Failure

Acute Injury/Failure

- Tender hepatomegaly

Chronic Liver Failure

- Ascites
- Caput medusae (dilated superficial periumbilical veins)
- Palmar erythema
- Spider angiomas
- Gynecomastia/testicular atrophy
- Parotid gland enlargement
- Muscular atrophy

Both Acute and Chronic Failure

- Jaundice
- Encephalopathy
- Asterixis

Table 7. Interpreting Results Of Laboratory Tests In Acute Hepatic Injury

Disease	Peak ALT, xURL[a]	AST: ALT ration	Peak billrubin, mg/dl	PT prolongation, s
Viral hepatitis	10-40	< 1	< 15	< 3
Alcoholic hepatitis	2-8	> 2	< 15	1-3
Toxic injury	> 40	> 1 early	< 5	> 5 (transient)
Ischemic injury	> 40	> 1 early	< 5	> 5 (transient)

[a] x URL, times the upper reference limit.

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liver. It is important to confirm that an elevation in AP is hepatobiliary in origin, since AP is also found in the placenta, ileal mucosa, kidney, and bone. This can be accomplished with 5-nucleotidase and gamma-glutamyl transferase (GGT) levels. GGT may be elevated by recent alcohol use, but only rarely is it elevated in patients with AP elevation from nonhepatic causes. It is rare for alkaline phosphatase to be greater than 3 times normal in the setting of acute hepatic injury.

Bilirubin

Bilirubin is elevated in cholestasis. An analysis of fractionated bilirubin should be carried out in all instances of hyperbilirubinemia to determine the proportions of unconjugated/indirect and conjugated/direct bilirubin. In acute liver injury, the pattern of direct hyperbilirubinemia is similar to that in obstructive jaundice — typically 50% of total bilirubin.[44] A predominance of indirect bilirubin suggests hemolysis or impaired conjugation. Greatly elevated bilirubin (> 17.5 mg/dL) has been associated with poor outcome in patients with acute hepatic failure in some studies but not others.[45] In viral hepatitis, a total bilirubin level above 15 mg/dL is a marker of disease severity and a more rapid progression to encephalopathy.[40]

Coagulation Studies

Coagulation studies, particularly the prothrombin time (PT)/international normalized ratio (INR), assess the liver's ability to synthesize clotting factors I, II, V, VII, and X. The INR is an important predictor of prognosis. A discriminant PT value greater than 20 seconds or an INR greater than 6.5 identifies patients at high risk for death.[40] In ischemic or toxic hepatic injury, coagulopathy typically peaks by 24 to 36 hours after injury and then quickly normalizes. In acetaminophen toxicity, initial PT prolongation is not independently associated with liver failure, but a persistently elevated or increasing value 4 days after ingestion is associated with liver failure.[46]

Albumin

Albumin is also produced by the liver, and low levels indicate a disruption in synthetic function. However, the prolonged half-life of albumin (20 days) may give falsely reassuring results in the evaluation of patients with ALF and hyperacute onset of symptoms (< 1 week).

Ammonia

Ammonia is elevated in liver failure as a result of impaired clearance. Although the correlation of ammonia level and degree of encephalopathy is controversial, it may be useful in the work-up of undifferentiated encephalopathy. The AASLD position paper on the management of ALF recommends including an ammonia measurement in the routine laboratory analysis of these patients.[6] Extremely high NH^3 levels are associated with edema and risk of herniation. Since most of the studies of ammonia have been based on arterial levels, an arterial sample should be considered if ammonia is to be measured.

Lactate Dehydrogenase

Lactate dehydrogenase is a nonspecific marker of cell injury; however, in cases of toxic or ischemic hepatic injury, levels can exceed those of AST at presentation.[47,48]

Chemistry Panel

A basic metabolic panel should also be assessed for derangements in acid-base status, sodium, and evidence of renal failure with associated hyperkalemia. In addition to diagnosing hepatorenal syndrome, creatinine is a component of a number of prognostic models. (**See the "Prognosis In ALF" section, page 9.**) Because liver failure patients are prone to hypoglycemia, serial glucose measurements with point-of-care testing are recommended.

Complete Blood Count

A complete blood count should be obtained for all patients with liver failure to detect infection, anemia, and thrombocytopenia. A type-and-screen or cross should be sent for all patients with reports of bleeding, depending on the degree of clinical stability.

Serologic Testing For Hepatitis

Serologic testing should be done for all patients with undifferentiated liver failure whose hepatitis status is unknown, particularly in cases of acute failure. Testing for hepatitis B virus should include a search for immunoglobulin M antibody to the hepatitis B core antigen (IgM anti-HBc), since this may be the only positive marker in acute infection. Other acute hepatitis markers include IgM antibodies to hepatitis A virus (HAV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV). Because anti-HCV and HCV RNA are present in both acute and chronic infection, there is no definitive way to distinguish between them, but positive HCV RNA in the absence of anti-HCV or markers of other hepatitis viruses is suggestive. Given that hepatitis D virus (HDV) is only pathologic in the setting of hepatitis B infection, the National Academy of Clinical Biochemistry Guidelines state that testing for HDV should be limited to patients with positive HBsAg, those at high risk for HDV infection (such as patients who abuse injection drugs), or those with an atypical, "biphasic" pattern to their clinical course.[40] Similarly, testing for hepatitis E (IgM anti-HEV) should be limited to patients with otherwise negative serologies who have recently traveled to areas where hepatitis is endemic.

Acetaminophen Level

The level of acetaminophen in plasma should be

measured in all patients with possible ALF. If the timing of ingestion and plasma level are known, the risk of hepatotoxicity can be determined using the Rumack-Matthew nomogram.[50]

Lactate

Lactic acid levels reflect global perfusion, and therefore rise when the body is forced to utilize anaerobic metabolism. Lactate levels have prognostic utility for mortality both in acetaminophen overdose[49] and in patients with undifferentiated ALF.[52]

Detection Of Less Common Etiologies

Less common causes of liver failure should be considered in certain patient populations. In such cases, the choice of laboratory tests is disease-specific. (**See Table 8.**)

Other laboratory tests that may assist in the work-up of patients with encephalopathy include arterial blood gas, toxicology screen, ethyl alcohol level, pregnancy test in females, and HIV antibody.

Table 8. Uncommon Etiologies Of Liver Failure

Cause	Clinical Characteristics	Laboratory Evaluation
Wilson disease	Patient under 40 years of age; unexplained liver disease (↑ AST, ALT, hepatomegaly); neuropsychiatric symptoms	Ceruloplasmin, serum copper, 24-h urinary copper excretion, total bilirubin:alkaline phosphatase ratio; slit-lamp examination for Kayser-Fleischer rings; MR imaging for any neuropsychiatric symptoms[53]
Autoimmune hepatitis	Women:men ratio = 3.6:1; no alternative diagnosis	Gamma-globulin or IgG, ANA, ASMA, anti-LKM1[54]
Hemochromatosis	Family history of liver or cardiac disease	Ferritin, TIBC, transferrin saturation
Budd-Chiari syndrome	Known hypercoagulability, ascites, abdominal pain, marked hepatomegaly	Imaging: CT scanning, Doppler ultrasound, or magnetic resonance venography
Herpes simplex virus (HSV) infection	Viral prodrome, mucosal ulcerations, pregnancy, impaired cellular immunity	Serum HSV antibody titers (IgM and IgG), serum viral cultures[55]
Epstein-Barr virus infection	Viral prodrome	Serum antibody
Varicella-zoster	Vesicular lesions	Serum antibody
Toxoplasmosis	Immunosuppression	Serum antibody, PCR

Abbreviations: ALT, alanine aminotransaminase; ANA, antineutrophil antibody; ASMA, anti–smooth muscle antibody; AST, aspartate aminotransaminase; CT, computed tomography; LKM1, liver kidney microsome 1; MR, magnetic resonance; PCR, polymerase chain reaction; TIBC, total iron-binding capacity.

Imaging In Liver Failure

Diagnostic imaging should be directed toward specific complaints. The patient with jaundice but no other evidence of liver failure should undergo ultrasound or CT scanning to detect any mechanical obstruction. In patients with shortness of breath, a chest x-ray should be obtained to look for evidence of pulmonary edema or pleural effusion. ALF concerning for Budd-Chiari syndrome should be evaluated by CT scan or ultrasound when available.

Prognosis And Treatment

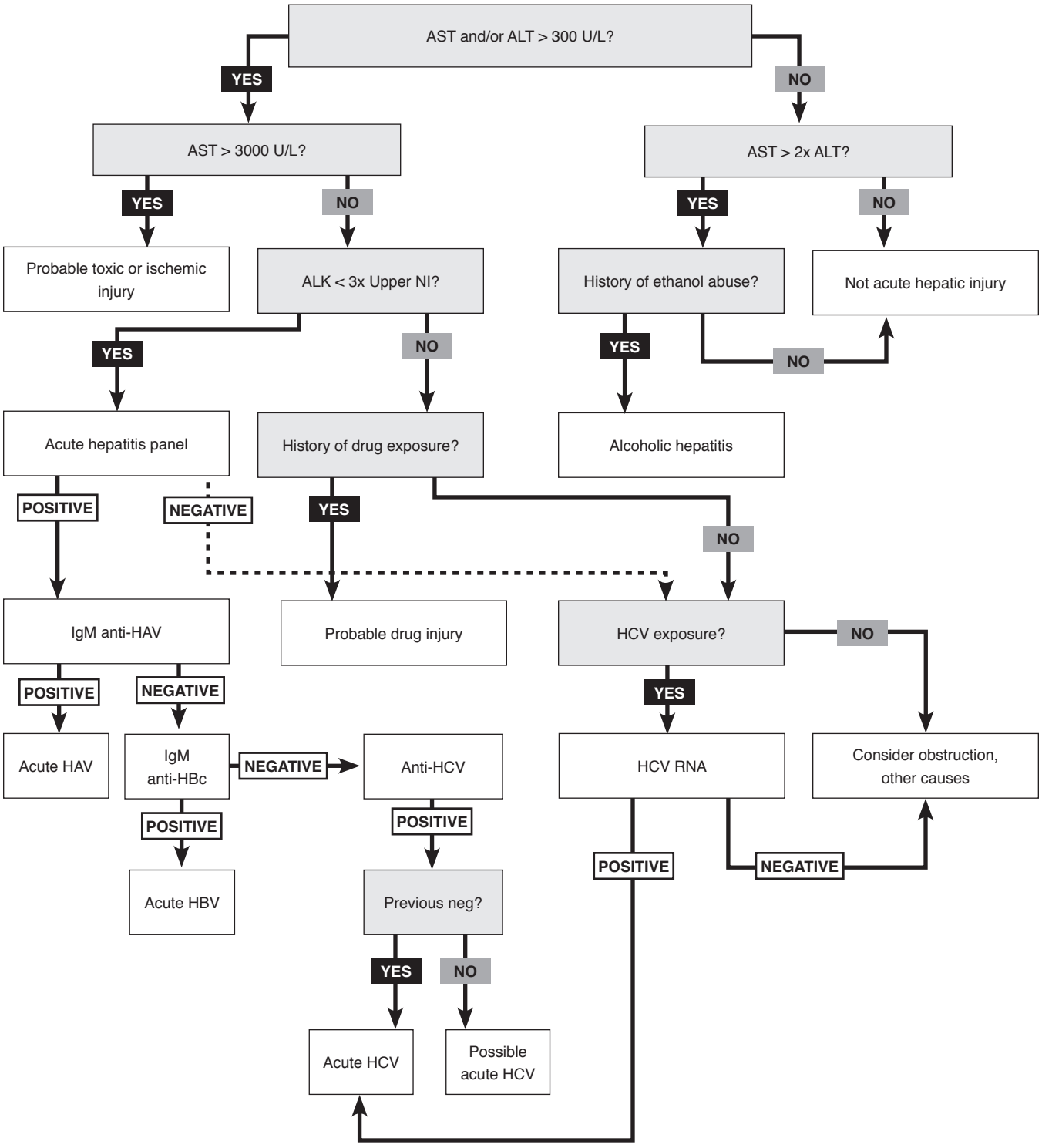
Prognosis In ALF

The prognosis for patients with ALF varies depending on the cause. Acetaminophen overdose, HAV infection, "shock liver," and pregnancy-related ALF are associated with the best spontaneous (non-transplanted) survival rates; patients with ALF due to Wilson disease, HBV infection, autoimmune hepatitis, Budd-Chiari syndrome, and malignancy fare worse.[10,14] The U.S. Acute Liver Failure Study Group has enrolled 1147 patients at 23 centers. Among all patients in their database, 45% recovered spontaneously, 44% were listed for transplantation, and 25% received a transplant; 10% of the total group and 50% of those listed for transplantation died while awaiting a donor organ. Overall mortality was 30%, compared with over 80% in the era prior to transplantation.[14] The most common causes of death in this group were cerebral edema and sepsis, followed by multiorgan system failure, cardiac arrhythmia/cardiac arrest, and respiratory failure. Coagulopathy in itself is not a frequent cause of death.

Several scoring systems have been developed to assess prognosis in liver failure. The Child-Turcotte-Pugh (CTP) system (**see Table 9, page 11**) was originally developed to assess risk associated with portocaval shunt surgery in variceal hemorrhage, but it is now widely used to assess prognosis in CLF.[56,57] Point values are associated with different laboratory values as well as the degree of encephalopathy. CTP scores of 5 to 6 result in a Class A diagnosis, 7 to 9 Class B, and 10 to 15 Class C. Mortality increases from class A to C.

More recently, the Model for End-Stage Liver Disease (MELD) score was developed as an adaptation of a scoring system to predict outcome in patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure. It was subsequently validated in different populations of patients with chronic hepatic failure[58] and is now applied to patients with acute hepatic failure as well, although it has not been validated in this population. The MELD score uses the INR, serum creatinine, and total bilirubin to calculate its numerical score, but the actual equation involves logarithmic calculations and is therefore less user-friendly than the CTP system. However, several

Clinical Pathway For Evaluation Of Patients With Suspected Acute Hepatic Injury



Abbreviations: ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M antibody; NI, normal.

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websites have online calculators available, such as the United Network For Organ Sharing official website (www.unos.org).[59,60]

In contrast with the above scales for CLF, the King's College Criteria (KCC) were developed to stratify risk in ALF. Several variables were found to be predictive of outcome and were then synthesized into criteria for transplantation.[45] For acetaminophen toxicity, these criteria were arterial pH less than 7.3 or the combination of PT longer than 100 seconds (~INR 6.5), serum creatinine greater than 3.5 mg/dL, and grade 3 or 4 encephalopathy. For ALF not caused by acetaminophen, transplantation was recommended for anyone with a PT longer than 100 seconds (~INR 6.5) or any 3 of the following findings: PT longer than 50 seconds (~INR 3.5), serum bilirubin greater than 17.5 mg/dL, cryptogenic or drug-induced liver failure, age less than 10 or over 40, or jaundice for more than 7 days before the onset of encephalopathy. However, in a more recent prospective trial, these latter 2 criteria were not found to be predictive.[9] In a meta-analysis of ALF due to acetaminophen, an arterial pH less than 7.3 was just as specific as the KCC, although neither was particularly sensitive and would therefore miss patients at risk for a poor outcome without transplantation.[61] Based on these data, the AASLD does not recommend that the ED clinician rely on these guidelines alone when determining a patient's risk.

Treatment Of ALF

Studies supporting nontransplant therapies for ALF are rare, which makes this disorder difficult to manage. The first decision facing the ED clinician is whether to transfer the patient to a transplant center. Although no studies directly address this issue, the AASLD recommends that the ED clinician establish early contact with a transplant center for patients with ALF, given the potential for rapid deterioration of their condition and the subsequent danger associated with transport to a transplant facility.[32] This is particularly true for patients with any of the poor prognostic indicators discussed above.

Table 9. Child-Turcotte-Pugh Scoring System For Severity Of Chronic Liver Disease

Clinical/Laboratory Finding	1 Point	2 Points	3 Points
Encephalopathy (grade)	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1 to 2	2 to 3	> 3
Albumin (g/dL)	3.5	2.8 to 3.5	< 2.8
Prothrombin time (sec prolonged) OR	1 to 4	4 to 6	> 6
INR	< 1.7	1.7 to 2.3	> 2.3
For primary biliary cirrhosis: bilirubin (mg/dL)	1 to 4	4 to 10	> 10

Critical Care Of The Patient With Liver Failure

ALF often progresses to multiorgan system involvement. Numerous therapies designed to maximize supportive care and prevent the previously discussed causes of mortality in ALF have been studied. Many of these interventions may also be applied to care of the critically ill patient with end-stage CLF.

Hepatic Encephalopathy, Cerebral Edema, And Elevated Intracranial Pressure

As discussed earlier, hyperammonemia is thought to play a role in hepatic encephalopathy, which in turn is related to cerebral edema, intracranial hypertension, and hypoxic brain injury. Nonabsorbable disaccharides such as lactulose are frequently administered to treat hepatic encephalopathy. In one retrospective case-control study by the U.S. Acute Liver Failure Study Group, lactulose therapy was associated with increased survival time but not with improvement in neurologic status or long-term outcome; this report suggested that lactulose may offer a bridge to transplantation.[62] In contrast, a recent Cochrane review concluded that nonabsorbable disaccharides (lactulose and lactitol) have no effect on mortality but may have an effect on encephalopathy. It also suggests that antibiotics such as neomycin might be superior to disaccharide treatment, although more data are required to confirm this suggestion.[63] A Cochrane meta-analysis of antibiotic treatment for hepatic encephalopathy is now under way. Data have failed to support treatment with branched-chain amino acids or dopaminergic agonists.[64,65] A transient improvement in degree of encephalopathy may be seen with flumazenil, but this treatment had no effect on ultimate recovery or survival; a Cochrane review concluded that more data are needed to recommend its routine use.[66]

In contrast with normal seizure management in the ED, the AASLD recommends that seizures be controlled with phenytoin primarily to prevent benzodiazepine oversedation due to decreased hepatic metabolism. However, a randomized, controlled trial of patients with ALF found that prophylactic phenytoin did not prevent seizures, cerebral edema, or the requirement for mechanical ventilation, nor did it improve survival.[67] Newer agents that undergo predominantly nonhepatic metabolism, such as levotiracetam, have not yet been studied.

Intracranial hypertension (as evident from neurologic signs) should be managed by elevating the head of the bed to 30° and a mannitol bolus (0.5 to 1.0 g/kg); its use has been shown to decrease ICP and improve survival in ALF patients.[68] Short-term hyperventilation may also be useful in critical situations

to prevent acute herniation. One study demonstrated a positive effect on restoring cerebral autoregulation (survival or neurologic outcomes not evaluated),[69] but another trial failed to show survival benefit with continuous hyperventilation.[70] Prophylactic hyperventilation is not recommended. The induction of hypernatremia (sodium 145-155 mmol/L) by the administration of 30% hypertonic saline may prevent the development of intracranial hypertension.[71] Several small studies have shown that hypothermia to 32° to 33ºC (89.6° to 91.4°F) will reduce intracranial pressure and can be used safely as a bridge until orthotopic liver transplantation can be performed[72,73]; however, no randomized, controlled trials have been carried out to evaluate this intervention. Corticosteroid treatment is not helpful.[68]

Coagulopathy

Despite the often profound coagulopathy associated with ALF, a well-designed randomized, controlled trial has shown that prophylactic normalization of the INR is not necessary unless a procedure other than paracentesis is planned.[74] The AASLD supports the use of vitamin K administration, although this therapy has not been specifically studied. Thrombocytopenia also occurs in patients with ALF. Data from the oncology literature support a platelet transfusion threshold of 10,000/µL for asymptomatic patients[75,76] and 50,000 to 70,000/µL for invasive procedures. Patients with active hemorrhage should receive platelets and fresh frozen plasma by transfusion. The use of recombinant factor VIIa in conjunction with fresh frozen plasma may be more effective in reversing coagulopathy[77] but requires further study.

Metabolic Dysfunction

Patients with liver damage are inherently prone to hypoglycemia and should be monitored frequently for this complication. Electrolyte derangement secondary to fluid shifts and multiorgan dysfunction is also common and should be monitored by means of serial laboratory analysis.

Specific Disease States

Acetaminophen Overdose

Acetaminophen overdose is now the most common cause of ALF in the US, as had previously been the case in Europe. It is the only truly reversible etiology of ALF, and it is the job of the ED clinician to evaluate the patient for possible acetaminophen toxicity and, if it is present, to begin therapy with N-acetylcysteine (NAC) as soon as possible. **Table 10** presents the American College of Emergency Physicians (ACEP) evidence-based clinical policy recommendations for treating patients with acetaminophen overdose.[78]

The decision to administer activated charcoal must be individualized based on likely time of ingestion and mental status; however, according to one randomized, controlled trial, administering activated charcoal just before treatment with NAC does not reduce its efficacy.[79] When the time and amount of ingestion are known, the indication for NAC can be determined using the Rumack-Matthew Nomogram.[50] However, this nomogram does not address ingestions that occurred longer than 24 hours before presentation, potential toxicity from chronic overdose, or therapeutic misadventure in the alcoholic or malnourished patient.

Although the efficacy of NAC (when it is administered within 8 hours of an acute ingestion) is well supported,[80] data also support its effect when given more than 10 hours after overdose (median delay 17 hours). In 1 retrospective study of 100 cases of acetaminophen-induced ALF, mortality was significantly reduced and progression to grade 3 or 4 encephalopathy decreased among patients who had been given NAC compared with those who were not.[81] NAC may be administered orally or intravenously depending on the patient's mental status and likelihood of compliance; there is no difference in efficacy between these 2 routes of administration.[82]

Based on the safety of NAC and its high rate of efficacy, AASLD guidelines recommend that NAC be given to all patients for whom the quantity of acetaminophen ingested, the serum acetaminophen level, or a rise in aminotransferase levels indicates progressive liver injury and to those for whom acetaminophen ingestion is a possibility or the circumstances of ingestion are unknown. While the qualifying quantity of acetaminophen ingested is not specified in this statement, a practice guideline by the American Association of Poison Control Centers for out-of-hospital management of nonsuicidal

Table 10. ACEP-Recommended Treatments In Acetaminophen Overdose

For patients with acute acetaminophen overdose for whom time of ingestion is known – ie, who can be risk-stratified using the Rumack-Matthew Nomogram[50]:

- Administer N-acetylcysteine (NAC) to patients who are at either *possible* or *probable* risk for hepatotoxicity as determined by nomogram, ideally within 8 to 10 hours after ingestion of the drug (Level B recommendation).
- Do *not* administer NAC to patients who are at no risk as determined by nomogram (Level B recommendation).

For patients with acetaminophen overdose who *cannot* be risk-stratified using the Rumack-Matthew Nomogram[50]:

- Administer NAC to patients with hepatic failure thought to be due to acetaminophen overdose (Level B recommendation).
- Administer NAC to patients who have hepatotoxicity thought to be due to acetaminophen or those who have suspected or known acetaminophen overdose, including repeated suprathera-peutic ingestions (Level C recommendation).

ingestion states that adults should be referred to the ED if there is an "acute, single, unintentional ingestion" of more than 10 g or 200 mg/kg (whichever is lower) or when the amount is unknown. Patients with "repeated supratherapeutic ingestion (RSTI) of acetaminophen" should be referred to the ED if they have ingested more than 10 g or 200 mg/kg (whichever is lower) over a 24-hour period OR if they have ingested more than 6 g or 150 mg/kg (whichever is lower) per 24-hour period during the preceding 48 hours or more. The threshold for patients at risk for acetaminophen hepatotoxicity at baseline (such as alcoholism) is more than 4 g or 100 mg/kg (whichever is lower) per day.[83] The Poison Control Center should be contacted with questions regarding treatment in specific cases.

Toxic Mushroom Poisoning

A common cause of mushroom poisoning is the ingestion of *Amanita phalloides.* Typically the patient will present with a history of mushroom ingestion as well as dramatic nausea, vomiting, cramping, and diarrheal symptoms. These symptoms are typically delayed by several hours from time of ingestion. *Amanita* hepatotoxicity carries a very high mortality. Two available treatments are used despite limited data to support their efficacy: penicillin G (300,000 to 1 million U/kg/day)[84] and silibinin (silymarin or milk thistle). Silibinin (or silymarin) is not available as a drug in the US but may be found in herbal extracts and supplements. In rare cases, individual doses of these agents may be obtained from Europe for clinical use. The AASLD maintains that these antidotes may be considered in cases of mushroom poisoning but that these patients should also be listed for transplantation. The Poison Control Center should be contacted in any case of suspected mushroom poisoning.

Viral Hepatitis

Treatment for ALF due to viral hepatitis is predominantly supportive, with early referral for possible liver transplantation. The use of treatments for chronic hepatitis B, such as the nucleoside/nucleotide analogues lamivudine, adefovir, entecavir, tenofovir, and telbivudine, has not been addressed in randomized, controlled trials in ALF. However, a recent National Institutes of Health consensus statement on the management of hepatitis B states that therapy with antiviral agents (not interferons) is indicated for patients with "rapid deterioration of liver function" as well as in those with decompensated cirrhosis (defined as cirrhosis with ascites, encephalopathy, or hemorrhage).[85] ALF secondary to herpes simplex virus (HSV) infection is rare, occurring mostly in immunosuppressed patients or pregnant women, and is not always accompanied by skin manifestations. In one case series, the authors recommend that empiric acyclovir be considered during the evaluation of any patient with ALF not due to acetaminophen, as well as for patients found to have the constellation of marked "transaminitis" with AST > ALT and mild hyperbilirubinemia ("anicteric hepatitis"), which has been associated with HSV hepatitis.[55] Acyclovir dosage recommendations have not been standardized for HSV hepatitis, but these authors describe a regimen of 10 mg/kg q8h. No studies of valacyclovir or famciclovir for this purpose have been published.

Other Etiologies

If autoimmune hepatitis is strongly suspected, corticosteroid therapy is indicated (prednisone 40-60 mg/day), although a liver biopsy should be considered to confirm the diagnosis.[54] If a diagnosis of Wilson disease is known and there is rapid progression to ALF, definitive treatment is exclusively transplantation. D-penicillamine treatment is contraindicated in patients with ALF and Wilson disease due to concern for hypersensitivity in this setting. Instead, plasmapheresis and exchange transfusion, hemofiltration, or dialysis with albumin are recommended as temporizing measures prior to transplantation.[53] Transplantation is rarely required in cases of "shock liver," in which hepatic dysfunction is compromised in the setting of severe congestive heart failure or profound hypotension. Optimization of cardiovascular support is the predominant treatment for this syndrome. In the case of hepatic vein thrombosis (Budd-Chiari syndrome), underlying malignancy should be excluded before the patient is listed for transplantation.

Emergency Complications Of Chronic Liver Failure

Ascites

Ascites is the most common major complication of cirrhosis.[86] The ED clinician most frequently encounters symptomatic or refractory ascites in the patient known to have cirrhosis; other causes include right-sided heart failure, nephrotic syndrome, pancreatitis, and malignancy.

To differentiate between causes of ascites and to treat symptomatic ascites, paracentesis should be performed. Indications for paracentesis in patients with cirrhosis include abdominal pain and shortness of breath from presumed compression. Paracentesis is a safe procedure with a low rate of serious complications (< 0.1%).[87] There is no absolute level of coagulopathy (INR or platelet level) beyond which paracentesis is contraindicated, nor are there data demonstrating benefit from the prophylactic transfusion of blood products prior to paracentesis; the AASLD does not recommend this practice.[7] The serum-ascites albumin gradient (SAAG) should be calculated from the fluid analysis. A SAAG of 1.1 g/dL or higher

supports a diagnosis of portal hypertension with 97% accuracy.[88] More-specialized tests, such as cytologic analysis, should be reserved for cases in which a nonhepatic etiology is likely. Large-volume paracentesis for tense ascites may lead to the syndrome of paracentesis-induced circulatory dysfunction (PICD), a largely silent activation of the renin-angiotensin-aldosterone system that nonetheless is associated with renal dysfunction, earlier recurrence of ascites, and higher mortality.[89] PICD may be prevented with plasma volume expansion; a recent trial demonstrated no increased benefit from albumin administration over that of normal saline in the prevention of PICD if the total volume of ascitic fluid removed was less than 6 L.[90] Frank hypotension is unusual unless the total volume of fluid removed is very high; 1 small study demonstrated no hemodynamic disturbances after a 5-L paracentesis,[91] whereas a total paracentesis protocol with an average volume of 8.2 L removed resulted in hypotension in 26% of patients. These data support a general threshold value for ascitic fluid removal of 6 L.[92]

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is traditionally managed with plasma expansion with albumin as well as hemodialysis as a bridge to orthotopic liver transplantation. Albumin may improve aspects of circulatory function such as peripheral vascular resistance, thereby lowering plasma renin activity.[93] Several vasoactive agents have also been studied in small trials. In 1 study, a protocol of albumin 20 to 40 g/d, along with octreotide and midodrine adjusted to produce an increase in mean arterial pressure of 15 mm Hg (with a starting dose of octreotide of 100 µg tid up to 200 µg tid and a starting dose of midodrine of 7.5 mg tid up to 12.5 mg tid), safely improved renal function.[94] Other treatments include the addition of splanchnic doses of dopamine or norepinephrine (0.5-3 mg/h IV)[95] to albumin.

Terlipressin, a vasopressin analogue, is not currently available in the US but is frequently studied in the treatment of HRS. A recent Cochrane review of terlipressin in HRS (irrespective of the use of additional agents such as albumin) concluded that terlipressin reduced mortality and improved renal function, although available data are still not sufficient to formulate treatment recommendations.[96] A more recent small, randomized, controlled trial demonstrated that terlipressin significantly improved renal function, but the results showed no survival benefit at 3 months.[97] Two open-label, randomized, controlled trials that compared norepinephrine (0.1-3.0 mg/h IV) to terlipressin (0.5-2 mg) reported similar outcomes,[98,99] suggesting that norepinephrine may be a viable alternative in US patients. Finally, a recent small, nonrandomized trial has suggested that paracentesis in volume-resuscitated patients with HRS improves renal function, although the effect is transient.[100] TIPS placement may be indicated in refractory cases.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP), an infection of ascitic fluid without a clear source such as perforation or abscess (secondary peritonitis), is diagnosed via an ascitic fluid polymorphonuclear cell count of 250 cells/mm^3 or higher or a positive fluid culture. Typical responsible organisms are *Klebsiella pneumoniae, Escherichia coli,* and *Streptoccocus pneumoniae.* Detection of SBP is important even in the absence of overt symptoms, since it is associated with increased mortality. While recent analyses of asymptomatic patients undergoing outpatient routine paracentesis have shown a low rate of occult SBP (0-3%),[101,102] analysis of serial samples from inpatients (who may be more similar to a symptomatic ED population) demonstrated a much higher rate (21%).[103] It is therefore recommended that ascitic fluid from all paracenteses be sent for cell count and differential counts. Culture bottles should be inoculated at the bedside for highest yield.[104] If secondary peritonitis is suspected, ascites fluid may also be analyzed to determine levels of glucose, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), and alkaline phosphatase (AP); fluid levels consistent with secondary peritonitis are glucose less than 50 mg/dL, LDH greater than the upper limit of normal for serum levels, CEA greater than 5 ng/mL, and AP greater than 240 U/L, or total protein exceeding 1 g/L.[105,106] Bedside testing for SBP using a leukocyte esterase reagent strip is becoming more common, especially in more austere settings. However, this method has not yet been standardized. A recent systematic review of 17 prospective trials showed wide variability in the characteristics of test strips – ie, sensitivity 45% to 100%, specificity 81% to 100%, positive predictive value 42% to 100%, and negative predictive value 87% to 100%.[107] The high negative predictive values reported in most analyses indicate the possible role of such testing as a means of ruling out SBP, but the method is still under investigation.

When the neutrophil count in ascitic fluid is 250 cell/mm^3 or higher, the patient should be treated empirically with antibiotics. Some patients have infection in the absence of neutrocytic fluid – a condition termed bacterascites. Those patients who progress to SBP will have signs of infection at the time of paracentesis[108]; outcomes are similar for both types of SBP patients. Therefore, patients with cirrhosis and ascites with clinical SBP (fever, leukocytosis, abdominal pain) but less than 250 neutrophils/mm^3 should be treated until culture results are known. Antibiotic regimens include cefotaxime (2 g IV q8h), ampicillin (2 g IV q4h) combined with tobramycin (1.75 mg/kg PO q8h), or oral ofloxacin (400 mg PO

bid) for less severe illness in patients who can take medication orally. Although 1 older study suggested that cefotaxime was superior to ampicillin/tobramycin,[109] a 2001 Cochrane Review concluded that there was insufficient evidence to support a particular antibiotic regimen based on 9 available randomized, controlled trials comparing antibiotic regimens (no placebo trials) for SBP.[110] Cefotaxime with albumin (1.5 g/kg IV on day 1 and 1.0 g/kg on day 3 of treatment) was shown in 1 study to be superior to cefotaxime alone,[111] although this finding has not been replicated.

Variceal Hemorrhage

Rupture of gastroesophageal varices is the most common fatal complication of cirrhosis. For the ED clinician, the diagnosis of likely variceal bleeding is made in the context of upper gastrointestinal (GI) bleeding in the patient with known or clinically apparent cirrhosis. In the case of gross hematemesis, the diagnosis of upper GI bleeding is clear. A report of coffee-ground emesis or melena is also likely to indicate an upper GI source.

For the diagnosis and assessment of bleeding severity, a nasogastric tube (NGT) may be indicated. When deciding whether to place an NGT, the ED clinician must balance the value of the information yielded against the substantial discomfort caused by the procedure, as well as the risk of damage to surrounding structures should the tube be improperly positioned. There is no literature to support the theoretical risk that NGT placement will further disrupt varices, so the procedure is generally considered to be safe in these circumstances.

In the patient with hematemesis, NGT placement does not yield additional information about the location of the bleed, but it may reveal the rate of ongoing bleeding. In addition, the NGT serves to clear gastric contents prior to endoscopy; however, since gastric aspiration may be performed at the time of endoscopy, and if vomiting does not threaten airway patency, such advance clearance may not be necessary. One retrospective study found that an uncleared fundal pool of blood at endoscopy was associated with increased rebleeding, number of units transfused, need for emergent surgery, and death[112]; however, these patients had residual fundal blood despite lavage and positioning, not because they did not have an NGT placed prior to endoscopy.

Intravenous erythromycin has been shown in 2 randomized, controlled trials to improve gastric emptying prior to esophagogastroduodenoscopy (EGD),[113,114] thus providing another means for achieving this goal. Other variables such as a drop in hemoglobin levels, tachycardia, and a reduction in blood pressure may serve as alternate indicators of the rate of blood loss. Even though results of randomized, controlled trials to address this issue are lacking, NGT placement is probably most useful in patients with hematemesis who are hemodynamically unstable, who have recurrent vomiting, and for whom endoscopy is likely to be delayed. In patients without hematemesis, the NGT serves to localize the site of bleeding proximal to the pylorus, thus supporting the need for EGD. In a patient with known varices and clinical evidence of upper GI bleeding without hematochezia (melena, an elevated blood urea nitrogen:creatinine ratio), the need for endoscopy to evaluate a variceal source based on history alone may obviate a diagnostic NGT. A final indication for NGT placement in cases of bright-red or coffee-ground emesis and possible ongoing bleeding would be to protect against the aspiration of gastric contents should a decline in mental status require intubation, but this issue has not been subjected to rigorous study.

For patients with variceal hemorrhage, aggressive primary resuscitation measures such as airway protection and large-bore IV access should be initiated immediately. Although crystalloids should be administered as needed for hypotension, blood transfusion should be arranged early to prevent significant hemodilution; replacement of the total volume of blood lost is not necessary and may be detrimental. In a Cochrane review that incorporated 1 multicenter randomized, controlled trial, recombinant factor VIIa was not shown to be of benefit.[115,116] Nonetheless, early consideration should be given to reversing coagulopathy with fresh frozen plasma and platelets based on the INR and platelet count. (**See the Coagulopathy section, page 12.**) In addition, transfusion of fresh frozen plasma should be considered independent of the INR for those patients who receive multiple units of factor-poor packed red cells.

Pharmacologic and endoscopic treatments are available for patients with bleeding varices. Medical therapy is based on acutely lowering the portal pressure by vasoconstriction of splanchnic arterial inflow and inhibition of local vasodilatory peptides, as well as systemic venodilation. Available regimens in the US include the somatostatin analogue octreotide and vasopressin accompanied by intravenous nitroglycerin to counteract any ischemic effects; it should be noted that this vasopressin regimen can be used for only 24 hours. (**See Table 11, page 16.**) A Cochrane meta-analysis of the effects of somatostatin analogues demonstrated no survival benefit, but failure of initial hemostasis was reduced and the amount of blood transfused was slightly decreased.[117]

In a Cochrane meta-analysis of 15 randomized, controlled trials comparing all types of medical therapy with endoscopic sclerotherapy, sclerotherapy was not superior to medical therapy for a variety of outcomes, including mortality after the initial treatment of variceal hemorrhage.[118] Although this analysis supports initial medical therapy, the AASLD recommends that EGD be performed within 12 hours to

definitively locate the source of hemorrhage.[8] EGD can help identify gastric-only varices, which differ from esophageal varices in terms of their endoscopic treatment. If endoscopy is to be performed, medical therapy should be continued, since it has been shown on meta-analysis to improve initial and 5-day hemostasis, although no effect on mortality has been demonstrated.[119]

Rescue techniques for uncontrolled or early, recurrent bleeding include TIPS or balloon tamponade. Balloon tamponade is a temporizing measure until a more definitive procedure such as TIPS can be performed. If balloon tamponade is performed, the patient should be intubated.

Severe bacterial infections are common in cirrhosis with variceal bleeding. According to 1 meta-analysis, prophylactic antibiotic administration decreases the risk of infection and increases survival,[120] so such prophylaxis should be initiated in the ED. (**See Table 12.**) Although the optimal antibiotic regimen remains to be determined, the AASLD recommends oral norfloxacin or intravenous quinolones for the majority of patients,[7] with ceftriaxone recommended for patients with more advanced cirrhosis (ie, Child-Turcotte-Pugh, Class B or C).[121]

Special Circumstances

Airway Management In Liver Failure

Airway management in the liver failure patient requires special attention to the cerebral edema and elevated intracranial pressure (ICP) associated with hepatic encephalopathy. Care should be taken to avoid further increases in ICP from airway stimulation. The traditional methods for blunting increased ICP utilized in head trauma patients may be employed here. Historically, ketamine was considered to be contraindicated in patients at risk for intracranial hypertension (and therefore for patients with liver failure) because of concerns about worsening ICP. However, small, nonrandomized studies have indicated that ketamine does not increase ICP in sedated patients with traumatic brain injury, brain tumor, or aneurysm — settings in which intracranial hypertension is likely.[122-124] In fact, these studies showed that ketamine lowered ICP while cerebral blood flow was not significantly affected. These studies do not address nonsedated patients (ie, those undergoing rapid-sequence intubation in which ketamine is the primary induction agent); however, these early results are promising. If larger studies demonstrate the same effect, ketamine may become the agent of choice for these patients, since the majority will be hypotensive and thus require an agent that can provide hemodynamic support.

None of the other medications typically employed for intubation are contraindicated in liver failure. However, results of a small study showing propofol to be useful for controlling elevated ICP in liver failure in the ICU setting suggest that this agent may be considered for induction of anesthesia, particularly since hepatic failure does not affect its metabolism.[125]

Patients with liver failure and variceal hemorrhage are at increased risk for aspiration during intubation due to the cathartic effect of blood in the stomach as well as the ongoing volume entering the stomach during active hemorrhage. This risk may be reduced by maintaining the patient in an upright position until just prior to intubation and by gastric evacuation via NGT. (**See the Variceal Hemorrhage section, page 15.**)

Pregnant Patients

Pregnant patients are more likely to develop serious sequelae of hepatitis E infection, with up to 20% mortality.[126] Pregnant patients are at increased risk of intrahepatic cholestasis, particularly in the third trimester. These patients present with pruritus and jaundice without other evidence of hepatic failure. They are at increased for complications such as preterm delivery and intrauterine demise.[127] Acute fatty liver of pregnancy (AFLP) and the related HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome are life-threatening complications of third-trimester pregnancy manifest as acute liver failure, for which the treatment is rapid delivery. Although delivery will improve outcome, postpartum transplantation may rarely be indicated.[16,128]

Controversies/Cutting Edge

As noted in this article, many interventions for ALF are available but are still the subject of some controversy because evidence to support them is lacking. Two areas of ongoing study and controversy have been selected for further discussion below.

Table 11. Pharmacologic Regimens For The Treatment Of Variceal Hemorrhage

Octreotide	50 µg IV bolus followed by 60 µg/h
Vasopressin	0.2 to 0.4 U/min (**for 24 hours only**)
PLUS	
Nitroglycerin	Starting dose of 40 µg/min IV (**for 24 hours only**)

Table 12. Prophylactic Antibiotic Regimens In Variceal Hemorrhage

Norfloxacin	400 mg bid PO bid
Ciprofloxacin	200 to 400 mg IV bid
Ceftriaxone	1g IV daily

Ten Risk Management Pitfalls To Avoid For Hepatic Failure

1. **"The patient needed central access, so I placed a subclavian line."**
   The subclavian vein is a noncompressible site and therefore should not be utilized in coagulopathy such as that seen in patients with liver failure. Ultrasound-guided internal jugular vein placement is preferable in this context; it allows for direct visualization of the vein to minimize arterial puncture, and the carotid is amenable to compression should arterial puncture transpire.

2. **"The patient was afebrile, so I did not send the paracentesis fluid for analysis."**
   Spontaneous bacterial peritonitis can have an indolent course, and associated abdominal pain may be mistaken for the discomfort of tense ascites. Peritoneal fluid should always be sent for analysis when a paracentesis is performed in the ED.

3. **"The patient had a seizure during his evaluation in the ED. The fingerstick glucose level was 20."**
   Patients with liver failure have impaired gluconeogenesis and are therefore prone to hypoglycemia. Check fingerstick glucose levels frequently and supplement IV fluids with dextrose.

4. **"The patient looked well, so I admitted him to a floor bed instead of the ICU."**
   ALF patients are critically ill and can deteriorate quickly; they should be admitted to high-visibility beds with a low threshold for ICU admission. In addition, contact with a transplant center should be made early to maximize transport safety should the patient need to be evaluated for possible liver transplantation.

5. **"I did not check an acetaminophen level because the patient said she did not ingest any medication."**
   Patients with suicidal intent may deny taking acetaminophen. Patients may also not be aware of the acetaminophen content of combined drugs. In a retrospective study of 1820 patients who ingested acetaminophen with suicidal intent or in whom ingestion was suspected because of altered mental status, 0.3% had a potentially toxic level of acetaminophen even though no history of ingestion had been suspected. Universal screening for acetaminophen level is recommended in cases of suicidal ingestion.[134]

6. **"I did not prescribe antibiotics for the variceal hemorrhage patient."**
   Even in the absence of acute infection at the time of bleeding, patients with variceal hemorrhage are at risk for serious bacterial infections. Administering prophylactic antibiotics increases survival.

7. **"I did not discuss risk of transmission with the patient with hepatitis C."**
   Although immediate stabilization takes priority in cases of ALF, it is important to discuss transmissibility with all patients who have infectious hepatitis. Hepatitis C is transmissible by sexual contact and is more transmissible than HIV via blood exposure, as would occur in patients sharing needles.

8. **"The pregnant patient did not have cholestasis, so I thought she was safe."**
   Hepatitis E may not produce laboratory evidence of cholestasis (a predominantly hepatocellular pattern may be seen), but it is still associated with high mortality among pregnant women. Pregnant patients with a background and history that raise concern about a possible acute infection with hepatitis A or E should be evaluated by an obstetrician.

9. **"The patient was becoming very agitated, so I gave her lorazepam to calm her. Then her blood pressure dropped."**
   Patients with liver failure are particularly susceptible to the effects of drugs that are metabolized in the liver. Most benzodiazepines undergo hepatic metabolism and thus may have a prolonged effect in these patients.

10. **"I did not recognize that the patient was altered—he comes in here drunk all the time."**
    Alcoholic patients are at risk for cirrhosis and hepatic encephalopathy. Special attention should be paid to the "chronically altered" frequent ED visitor, and the ED clinician should consider further workup if the apparently intoxicated patient does not regain an appropriate mental status within a short period of time.

N-Acetylcysteine (NAC) In Liver Failure Not Caused By Acetaminophen

The use of NAC in acetaminophen toxicity is well-supported. In addition, because of its effectiveness in scavenging oxygen free radicals and improving glutathione stores, NAC has been suggested as a "liver tonic" for patients with liver damage. Some studies have suggested that NAC provides circulatory support by increasing oxygen delivery and consumption and improving cardiac index and mean arterial pressure in ALF due to acetaminophen (ie, those for whom an earlier NAC treatment window had passed) or ALF due to other causes.[129] NAC has also been shown to increase the cardiac index and hepatic blood flow in patients with septic shock without liver failure.[130] However, another study using different measurements of oxygen delivery did not demonstrate improvements in hemodynamics or in oxygen delivery or consumption with NAC.[131]

A systematic review of published articles on the use of NAC in ALF not related to acetaminophen concluded that the data were not sufficient to recommend its routine employment in this setting.[132] Since the efficacy of NAC in nonacetaminophen-related ALF is still under investigation, it may eventually be borne out by the results of future studies.

Artificial Liver Support Systems

Many review articles over the years have mentioned bioartificial liver support devices as an "up-and-coming" potential bridge to transplantation. However, data demonstrating a survival benefit with these devices are scarce, and the methodologies involved are still under investigation. A Cochrane review of bioartificial and artificial devices has concluded that they may offer a survival benefit in acute-on-chronic liver failure but not in ALF; further investigation was advised before such approaches can be routinely implemented.[133] Studies to evaluate these support systems are ongoing.

Disposition

Any patient with ALF should be admitted to the hospital. As noted earlier, the AASLD recommends admission to the ICU for all patients with ALF based on their risk of rapid deterioration. Early contact with a transplant center should also be established (in cases of grade 1 or 2 encephalopathy) to enable triage for transplantation as well as early transfer before the patient requires airway protection or becomes otherwise unstable. Patients who present with variceal bleeding should also be admitted, with their level of care determined by their overall clinical picture. Patients with symptomatic ascites may be discharged with close follow-up after peritoneal fluid analysis rules out spontaneous bacterial peritonitis, provided that their symptoms improve after paracentesis and they have no signs of encephalopathy. Collateral information regarding the patient's baseline mental status is critical to detecting subtle signs of encephalopathy.

Summary

ALF is a life-threatening disorder that requires immediate recognition by the ED clinician so that supportive measures, treatment of reversible causes, and possible transfer to a transplant facility can be initiated. ALF patients have the potential to decompensate quickly, which will require intubation, management of intracranial hypertension, and treatments for coagulopathy, hypoglycemia, and seizures. Acute complications in patients known to have cirrhosis are frequently seen in the ED; patients with respiratory symptoms or other discomfort from tense ascites should undergo paracentesis and surveillance for spontaneous bacterial peritonitis. Variceal bleeding is a lethal complication of CLF and should be treated aggressively with medical and endoscopic therapy as well as antibiotics. Swift intervention in these ill patients can stabilize them long enough to allow recovery or evaluation for transplantation.

Case Conclusions

Your 40-year-old male patient on isoniazid has developed ALF from an idiosyncratic reaction to the drug — a diagnosis confirmed by his INR of 2.0 and elevated AST, ALT, and bilirubin. He has grade 1 encephalopathy. After moving him to a high-visibility bed in the ED, starting IV fluids via peripheral IV, and evaluating his glucose and electrolyte levels, you contact the transplant center located an hour away and arrange for an advanced life support ambulance to transport the patient.

Your CLF patient has a massive GI bleed, most likely due to varices. After establishing large-bore IV access, administering an initial bolus of crystalloid, and calling for blood, you start treatment with octreotide and ceftriaxone. You arrange for urgent endoscopy and admit the patient to the ICU with an improved blood pressure.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most

informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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Practice Recommendations

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1. Which of the following is a diagnostic criterion for ALF?
a. ALT > 3500 U/L
b. Disease duration of < 1 year
c. INR ≥ 1.5
d. Total bilirubin > 3 mg/dL

2. Which of the following is the most common cause of ALF in the United States?
a. Acetaminophen toxicity
b. Drug reactions
c. Hepatitis A
d. Ischemic injury

3. What is the threshold number of polymorphonuclear cells per mm^3 at which SBP may be diagnosed?
a. 100
b. 150
c. 250
d. 500

4. Which of the following is an appropriate antibiotic regimen for the treatment of SBP?
a. Amoxicillin-clavulanic acid (500 mg PO q12h)
b. Cefotaxime 2 g IV q8h
c. Clindamycin 600 mg IV q8h
d. Trimethoprim-sulfamethoxazole (1 DS tab PO q12h)

5. Which of the following is NOT a recommended treatment for intracranial hypertension in liver failure?
a. Corticosteroids
b. Head-of-bed elevation (30°)
c. Hypertonic saline
d. Mannitol

6. Which of the following is true about the performance of paracentesis?
a. Indications include abdominal pain and shortness of breath.
b. Paracentesis is contraindicated for an INR > 2.0.
c. Prophylactic transfusion of albumin is recommended.
d. Removal of greater than 4 L ascitic fluid is associated with hypotension.

7. Which of the following is true regarding toxic mushroom poisoning?
a. Available medical treatments include penicillin G and silymarin.
b. Symptom onset occurs immediately after ingestion.
c. The associated mortality is low.
d. Typical symptoms include fever and constipation.

8. After initial resuscitation, what additional treatment is recommended for variceal hemorrhage?
a Esophageal manometry
b. Prophylactic antibiotics
c. Pulsed-dose steroids
d. Transfusion with albumin

9. Which of the following statements regarding coagulopathy related to liver failure is true?
a. It is a frequent cause of death in liver failure.
b. Platelet numbers are not typically affected.
c. Vitamin K is contraindicated in liver failure.
d. The transfusion threshold for asymptomatic patients is 10,000/µL.

10. Which of the following statements regarding drug-induced hepatic failure is true?
a. Acetaminophen is the only hepatotoxin with a direct antidote.
b. Herbal extracts have not been associated with hepatotoxicity.
c. It is associated with a comparatively high transplant-free survival rate.
d. Idiosyncratic drug reactions typically occur after > 1 year of continuous use.

March 2010 Errata

In the March 2010 issue of Emergency Medicine Practice, "Oncologic Emergencies, Part II: Neutropenic Fever, Tumor Lysis Syndrome, And Hypercalcemia Of Malignancy," the peer reviewers were misidentified. The correct peer reviewers were:

Marc Borenstein, MD, FACEP, FACP
Department Chair and Program Director, Emergency Medicine Residency Program, Newark Beth Israel Medical Center, Newark, NJ

Michael Johnston, MD, FAAP
Assistant Professor of Emergency Medicine and Pediatrics, Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN

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Hepatic Failure: An Evidence-Based Approach In The Emergency Department

Bailey C, Hern HG Jr. April 2010, Volume 12; Number 4

This issue of Emergency Medicine Practice focuses on the management of acute liver failure and the acutely symptomatic cirrhotic patient. *For a more detailed discussion of this topic, including figures and tables, clinical pathways, and other considerations not noted here, please see the complete issue on the EB Medicine website at www.ebmedicine.net/topics.*

Key Points	Comments
Acute liver failure (ALF) is a rapidly progressive serious illness; prognosis varies with etiology. Acetaminophen intoxication and viral hepatitis are common causes.	Acetaminophen overdose, hepatitis A, "shock liver," and pregnancy-related ALF have the best spontaneous (non-transplanted) survival; ALF due to Wilson disease, hepatitis B, autoimmune hepatitis, Budd-Chiari syndrome, and malignancy fare worse.[8,12]
Liver failure is manifested by characteristic laboratory tests including evidence of hepatocellular injury, cholestasis, coagulopathy, and hyperammonemia.	While the correlation of ammonia with degree of encephalopathy is controversial, it may be useful in the workup of undifferentiated encephalopathy. The AASLD position paper on the management of acute liver failure recommends its inclusion in the routine laboratory analysis of these patients.[46]
Acute liver failure patients may develop hemodynamic instability, cerebral edema, seizures, and hepatorenal syndrome. Reassess vital signs and mental status frequently.	Intracranial hypertension (IH) (as appreciated via neurological signs) should be managed with head-of-bed elevation (30˚) and mannitol bolus (0.5-1g/kg); its use has been shown to decrease intracranial pressure and improve survival in ALF patients.[64] Hypernatremia (Na 145-155), produced via administration of 30% hypertonic saline, may prevent development of IH.[67]
Patients with refractory ascites are susceptible to spontaneous bacterial peritonitis (SBP); ascitic fluid should be sent for analysis during therapeutic paracentesis.	While recent analyses of asymptomatic patients undergoing outpatient routine paracentesis have shown a low rate (0-3%) of occult SBP,[97,98] analysis of serial samples from inpatients (who may be more similar to a symptomatic emergency department population) demonstrated a much higher rate (21%).[99]
Patients with cirrhosis and ascites with clinical SBP (fever, leukocytosis, abdominal pain) but < 250 cells/mm^3 should be treated until culture results are known. Antibiotic regimens include cefotaxime (2g IV q8h), ampicillin 2g IV q4h combined with tobramycin 1.75 mg/kg q8 hr, or oral ofloxacin (400 mg bid) for less severe illness in patients who can take PO.	While 1 older study suggests that cefotaxime is superior to ampicillin/tobramycin,[105] a 2001 Cochrane Review concluded that there was insufficient evidence to support a particular antibiotic regimen, based on 9 available randomized controlled trials comparing antibiotic regimens (no placebo trials) for SBP.[106]
Variceal hemorrhage should be managed with hemodynamic support, vasoactive agents, and endoscopy. Medical therapy regimens in the US include octreotide (50 µg bolus then 60 µg/hr) and vasopression (0.2-0.4 units/min) accompanied by IV nitroglycerin (starting dose 40 µg/min) to counteract ischemic effects.	A Cochrane meta-analysis of the effects of somatostatin analogues did not demonstrate a mortality benefit, but there was a reduced failure of initial hemostasis and a slightly decreased amount of blood transfused.[113] A Cochrane meta-analysis of 15 RCTs comparing all types of medical therapy with endoscopic sclerotherapy demonstrated that sclerotherapy was not superior to medical therapy on a variety of outcomes including mortality for initial treatment of variceal hemorrhage.[114]

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These references are excerpted from the original manuscript. For additional references and information on this topic, see the full text article at ebmedicine.net.

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